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DOCUMENT-IDENTIFIER: US 6638621 B2
TITLE: Coated particles, methods of making and using

Brief Summary Text (5):
Two particle technologies-polymer-coated particles and liposomes--are of general interest.

Brief Summary Text (6):
Polymer-coated particles have been very important in the development of useful microparticles and of controlled-release vehicles generally. In certain circumstances polymers have coating and spreading properties that provide for good encapsulation of various matrices, and they are available in a range of chemistries and molecular weights. Certain polymeric coatings are of such utility and low toxicity that approval has been obtained for their use even in injectable products within the pharmaceutical industry, most notably polylactic-glycolic acid copolymers, and the usefulness of polymeric coatings in oral products is well-established, as in the cases of Eudragits, gelatin, and a number of natural gums. In many settings in fact, microparticle coatings are tacitly assumed to be polymers.

Brief Summary Text (7):
However, polymer-coated particles exhibit several limitations, as the flattened and diffuse response of their polymer coatings to chemical and physical triggers indicates. This is due to two factors. First, the high molecular weight of polymers reduces their diffusion coefficients and their kinetics of solubilization. Second, the neighboring group effect broadens the curves representing the chemical responses to triggers such as, inter alia, pH, salinity, oxidation and reduction, ionization, etc. (The neighboring group effect indicates that chemical changes in one monomeric unit of a polymer significantly alter the parameters governing chemical transitions in each of the neighboring monomeric units.) Further, most polymers are collections of chemical species of broadened molecular weight distribution. In addition, for a given application of the polymer coated particle only a limited number of suitable polymers are frequently available. This is due to a number of factors: regulatory issues: the coating processes often entail harsh chemical and/or physical conditions, such as solvents, free radicals, elevated temperatures, dessication or drying, and/or macroscopic shearing forces needed to form the particles; the limited mechanical and thermal stabilities of the polymeric coatings in industrial applications; and adverse environmental impacts in large scale applications of polymer-coated particles, such as in agricultural use.

Brief Summary Text (8):
Liposomes also exhibit a number of limitations. Among these are their physical and chemical instabilities. The release of a material disposed within the liposome is usually dependent on the destabilization of the structure of the liposome. In particular, the absence of porosity precludes the pore-controlled release of such materials. The dual requirements of 1) physical stability of the liposome until release is desired on the one hand and 2) release of materials by bilayer destabilization when release is desired on the other, are problematic. (The term liposomes is frequently interchanged with the term vesicles and is usually reserved for vesicles of glycerophospholipids or other natural lipids. Vesicles are self-supported closed bilayer assemblies of several thousand lipid molecules (amphiphiles) that enclose an aqueous interior volume. The lipid bilayer is a

two-dimensional fluid composed of lipids with their hydrophilic head groups exposed to the aqueous solution and their hydrophobic tails aggregated to exclude water. The bilayer structure is highly ordered yet dynamic because of the rapid lateral motion of the lipids within the plane of each half of the bilayer.) See O'Brien. D. F. and Rarnaswami, V. (1989) in Mark-Bikales-Overberger-Menges Encyclopedia of Polymer Science and Engineering. Vol. 17, Ed. John Wiley & Inc., p. 108.

Detailed Description Text (14):
Very effective systems for satisfying such solubilization requirements are provided by lipid--water systems, in which microdomains are present which are very high in water content, and simultaneously hydrophobic domains are in very close contact with the aqueous domains. The presence of aqueous domains circumvents precipitation tendencies encountered in systems where water structure is interrupted by the presence of high loadings of co-solvents or co-solutes, as, for example, in concentrated aqueous polymer solutions. At the same time the proximity of hydrophobic domains provides for effective solubilization of amphiphilic compounds (and hydrophobic as well).

Detailed Description Text (17):
Polar: polar compounds (such as water) and polar moieties (such as the charged head groups on ionic surfactants or on lipids) are water-loving or hydrophilic: "polar" and "hydrophilic" in the context of the present invention are essentially synonymous. In terms of solvents, water is not the only polar solvent. Others of importance in the context of the present Invention are: glycerol, ethylene glycol, formamide, N-methyl formamide, dimethylformamide, ethylammonium nitrate, acetamide, N-methylacetamide, dimethylacetamide, N-methyl sydnone, and polyethylene glycol. Note that one of these (polyethylene glycol) is actually a polymer, thereby illustrating the range of possibilities. At sufficiently low molecular weights, polyethvlene glycol (PEG) is a liquid, and although PEG has not been extensively studied as a polar solvent in combination with surfactants, it has been found that PEG does form nanostructured liquid phases and liquid crystalline phases in combination with, for example, surfactants such as BRIJ-type surfactants, which are nonionic surfactants with PEG head groups ether-linked to alkane chains. More generally, in terms of polar groups in hydrophilic and amphiphilic molecules (including but not limited to polar solvents and surfactants), a number of polar groups are tabulated below, in the discussion of which polar groups are operative as surfactant head groups and which are not.

Detailed Description Text (18):
Apolar. An apolar compound is a compound that has no dominant polar group. Apolar (or hydrophobic, or alternatively, "lipophilic") compounds include not only the paraffinic/hydrocarbon/alkane chains of surfactants, but also modifications of them, such as perfluorinated alkanes, as well as other hydrophobic groups such as the fused-ring structure in cholic acid as found in bile salt surfactants, or phenyl groups as form a portion of the apolar group in Triton-type surfactants, and oligomer and polymer chains that run the gamut from polyethylene (which represents a long alkane chain) to hydrophobic polymers such as hydrophobic polypeptide chains in novel peptide-based surfactants that have been investigated. A listing of some apolar groups and compounds is given below, in the discussion of useful components of the nanostructured phase interior. An apolar compound will be lacking in polar groups, a tabulation of which is included herein, and will generally have an octanol-water partition coefficient greater than about 100, and usually greater than about 1,000.

Detailed Description Text (29):
In addition to the polar head group, a surfactant requires an apolar group, and again there are guidelines for an effective apolar group. For alkane chains, which are of course the most common, if n is the number of carbons, then n must be at least 6 for surfactant association behavior to occur, although at least 8 or 10 is the usual case. Interestingly octylamine, with n=8 and the amine head group which is just polar enough to be effective as a head group, exhibits a lamellar phase with water at ambient temperature, as well as a nanostructured L2 phase. Warnhelm. T., Bergenstahl. B., Henriksson. U., Malmvik. A.-C. and Nilsson. P. (1987) J. of Colloid and Interface Sci. 118:233. Branched hydrocarbons yield basically the same requirement on the low n end: for example, sodium 2-ethylhexylsulfate exhibits a

full range of liquid crystalline phases. Winsor, P. A. (1968) Chem. Rev. 68:1. However, the two cases of linear and branched hydrocarbons are vastly different on the high n side. With linear, saturated alkane chains, the tendency to crystallize is such that for n greater than about 18, the Krafft temperature becomes high and the temperature range of nanostructured liquid and liquid crystalline phases increases to high temperatures, near or exceeding 100.degree. C. In the context of the present invention, for most applications this renders these surfactants considerably less useful than those with n between 8 and 18. With the introduction of unsaturation or branching in the chains, the range of n can increase dramatically. The case of unsaturation can be illustrated with the case of lipids derived from fish oils, where chains with 22 carbons can have extremely low melting points due to the presence of as many as 6 double bonds, as in docosahexadienoic acid and its derivatives, which include monoglycerides, soaps, etc. Furthermore, polybutadiene of very high MW is an elastomeric polymer at ambient temperature, and block copolymers with polybutadiene blocks are well known to yield nanostructured liquid crystals. Similarly, with the introduction of branching one can produce hydrocarbon polymers such as polypropyleneoxide (PPO) which serves as the hydrophobic block in a number of amphiphilic block copolymer surfactants of great importance, such as the Pluronic series of surfactants. Substitution of fluorine for hydrogen, in particular the use of perfluorinated chains, in surfactants generally lowers the requirement on the minimal value of n, as exemplified by lithium perfluorooctanoate (n=8), which displays a full range of liquid crystalline phases, including an intermediate phase which is fairly rare in surfactant systems. As discussed elsewhere, other hydrophobic groups, such as the fused-ring structure in the cholate soaps (bile salts), also serve as effective apolar groups, although such cases must generally be treated on a case by case basis in terms of determining whether a particular hydrophobic group will yield surfactant behavior.

Detailed Description Text (30):
For single-component block copolymers, relatively simple mean-field statistical theories are sufficient to predict when nanostructure liquid phase and liquid crystalline phase materials will occur and these are quite general over a wide range of block copolymers. If .chi. is the FloryHuzuins interaction parameter between polymer blocks A and B, and N is the total index of polymerization defined as the number of statistical units or monomer units in the polymer chain, consistently with the definition of the interaction parameter of the block copolymer, then nanostructure liquid and liquid crystalline phases are expected when the product .chi. N is greater than 10.5. Leibler, L. (1980) Macromolecules 13:1602. For values comparable to but larger than this critical value of 10.5, ordered nanostructured (liquid crystalline) phases can occur, including ever, bicontinuous cubic phases. Hajduk,. D. A., Harper, P. E., Gruner, S. M., Honeker, C. C., Kim, G., Thomas, E. L. and Fetters, L. J. (1994) Macromolecules 27:4063.

Detailed Description Text (50):
For L1 phases in block copolymer-based systems, this same SAXS analysis holds. In contrast, NMR bandshape and self-diffusion measurements in general do not carry over, nor do surface tension measurements. However, vapor transport measurements have been used in the past in place of NMR self-diffusion, in particular, if one can find a gas which is preferentially soluble in one of the domain types but not in the other(s), then one can test for continuity of those domains by measuring the transport of that gas through the sample. If this is possible, then transport through the continuous domains (type B) in the micellar phase should be only slightly slower than that in the pure B polymer, whereas gas transport for a gas confined to A domains should be very low.

Detailed Description Text (51):
The shear modulus of a block copolymer-based micellar phase is determined largely by that of the polymer block forming the continuous domains, polymer B in our convention. Thus, for example, in a PS-PI diblock which is 10% PS, so that PS micelles form in a continuous PI matrix, the shear modulus would be close to that of pure polyisoprene with only a slight increase due to the presence of the PS micelles. Interestingly, in the reverse case, with 90% PS and thus PI micelles in a continuous PS matrix, the elastomeric PI micelles can provide a shock-absorbing component which can improve the fracture characteristics over those of pure, glassy polystyrene.

Detailed Description Text (83):
For normal discrete cubic phases in surfactant-water systems: 1. Viscosity is high, much more viscous than the lamellar phase and even more viscous than typical normal hexagonal phases. Most cubic phase have viscosities in the millions of centipoise, whether discrete or bicontinuous. 2. Also in common with the bicontinuous cubic phases, there is no splitting in the NMR bandshape, only a single isotropic peak. 3. In terms of phase behavior, the normal discrete cubic phase generally occurs at fairly low surfactant concentrations in single-tailed surfactant water systems, typically on the order of 40% surfactant with ionic surfactants. Usually the normal discrete cubic phase region is between normal micellar and normal hexagonal phase regions, which along with its high viscosity and non-birefringence make its determination fairly simple. In double-tailed surfactants, it generally does not occur at all in the binary surfactant-water system. For discrete cubic phases in single-component block copolymer systems, the terms "normal" and "reversed" do not generally apply (although in the case where one block is polar and the other apolar, these qualifiers could be applied in principle). The shear modulus in such a discrete cubic phase is generally dependent almost entirely on the shear modulus of the polymer that forms the blocks in the continuous phase. In terms of phase behavior, the discrete cubic phases generally occur at very low volume fractions of one or other of the two blocks, on the order of 20% or less.

Detailed Description Text (103):
Suitable block copolymers are those composed of two or more mutually immiscible blocks from the following classes of polymers: polydienes, polyallenes, polyacrylics and polymethacrylics (including polyacrylic acids, polymethacrylic acids, polyacrylates, polymethacrylates, polydisubstituted esters, polyacrylamides, polymethacrylamides, etc.), polyvinyl ethers, polyvinyl alcohols, polyacetals, polyvinyl ketones, polyvinylhalides, polyvinyl nitriles, polyvinyl esters, polystyrenes, polyphenylenes, polyoxides, polycarbonates, polyesters, polyanhydrides, polyurethanes, polysulfonates, polysiloxane, polysulfides, polysulfones, polyamides, polyhydrazides, polyureas, polycarbodiimides, polyphosphazenes, polysilanes, polysilazanes, polybenzoxazoles, polyoxadiazoles, polyoxadiazoiidines, polythiazoles, polybenzothiazoles, polypyromellitimides, polyquinoxalines, polybenzimidazoles, polypiperazines, cellulose derivatives, alginic acid and its salts, chitin, chitosan, glycogen, heparin, pectin, polyphosphorus nitrile chloride, polytri-n-butyl tin fluoride, polyphosphoryldimethylamide, poly-2,5-selenienylene, poly-4-n-butylpyridinium bromide, poly-2-N-methylpyridinium iodide, polyallylammonium chloride, and polysodium-sulfonate-trimethylene oxyethylene. Preferred polymer blocks are polyethylene oxide, polypropylene oxide, polybutadiene, polyisoprene, polychlorobutadiene, polyacetylene, polyacrylic acid and its salts, polymethacrylic acid and its salts, polyitaconic acid and its salts, polymethylacrylate, polvethylacrylate, polybutylacrylate, polymethylmethacrylate, polypropylmethacrylate, poly-N-vinyl carbazole, polyacrylamide, polyisopropylacrylamide, polymethacrylamide, polyacrylonitrile, polyvinyl acetate, polyvinyl caprylate, polystyrene, poly-alpha-methylstyrene, polystyrene sulfonic acid and its salts, polybromostyrene, polybutyleneoxide, polyacrolein, polydimethylsiloxane, polyvinyl pyridine, polyvinyl pyrrolidone, polyoxy-tetramethylene, polydimethylfulvene, polymethylphenylsiloxane, polycyclopentadienylene vinylene, polyalkylthiophene, polyalkyl-p-phenylene, polyethylene-altpropylene, polynorbornene, poly-5-((trimethylsiloxy)methyl)norbornene, polythiophenylene, heparin, pectin, chitin, chitosan, and alginic acid and its salts. Especially preferred block copolymers are polystyrene-b-butadiene, polystyrene-b-isoprene, polystyrene-b-styrenesulfonic acid, polyethyleneoxide-b-propyleneoxide, polystyrene-b-dimethylsiloxane, polyethyleneoxide-b-styrene, polynorborene-b-5-((trimethylsiloxy)methyl)norbornene, polyacetylene-b-5((trimethylsiloxy)methyl)norbornene, polyacetylene-b-norbornene, polyethyleneoxide-b-norbornene, polybutyleneoxide-b-ethyleneoxide, polyethyleneoxide-b-siloxane, and the triblock copolymer polyisoprene-b-styrene-b-2-vinylpyridine.

Detailed Description Text (106):
Suitable third components (hydrophobes or non-surfactant amphiphiles), include:

n-alkane, where n is from 6 to 20, including branched, unsaturated, and substituted variants (alkenes, chloroalkanes, etc.), cholesterol and related compounds, terpenes, diterpenes, triterpenes, fatty alcohols, fatty acids, aromatics, cyclohexanes, bicyclics such as naphthalenes and naphthol, quinolines and benzoquinolines, etc., tricyclics such as carbazole, phenothiazine, etc., pigments, chlorophyll, sterols, triglycerides, sucrose fatty acid esters (such as Olestra.TM.), natural oil extracts (such as clove oil, anise oil, cinnamon oil, coriander oil, eucalyptus oil, peppermint oil), wax, bilirubin, bromine, iodine, hydrophobic and amphiphilic proteins and polypeptides (including gramicidin, casein, receptor proteins, lipid-anchored proteins, etc.), local anesthetics (such as butacaine, ecgonine, procaine, etc.), and low-molecular weight hydrophobic polymers (see listing of polymers above). Especially preferred third components are: anise oil, clove oil, coriander oil, cinnamon oil, eucalyptus oil, peppermint oil, beeswax, benzoin, benzyl alcohol, benzyl benzoate, naphthol, capsaicin, cetearyl alcohol, cetyl alcohol, cinnamaldehyde, cocoa butter, coconut oil, cottonseed oil (hydrogenated), cyclohexane, cyclomethicone, dibutyl phthalate, dibutyl sebacate, diocryl phthalate, DIPAC, ethyl phthalate, ethyl vanillin, eugenol, fumaric acid, glyceryl distearate, menthol, methyl acrylate, methyl salicylate, myristyl alcohol, oleic acid, oleyl alcohol, benzyl chloride, paraffin, peanut oil, piperonal, rapeseed oil, rosin, sesame oil, sorbitan fatty acid esters, squalane, squalene, stearic acid, triacetin, trimyristin, vanillin, and vitamin E.

Detailed Description Text (116):
Nonlamellar amorphous and semi-crystalline materials are materials comprising non-crystalline domains (or lacking crystallinity altogether) in which strong atomic interactions exist in all three dimensions. In the amorphous trehalose that provides the coating in Example 40, for example, the packing of these sugar molecules and the multiple hydrogen bonds that each individual molecule can participate in make this a compound that exhibits strong interactions in all three dimensions (and the amorphous property rules out any lamellar-type structure). Similarly amorphous PLGA has strong interactions between the carboxyl groups across neighboring polymer chains which, since the material is optically isotropic, are not limited to two dimensions. The release of a coating in a PLGA-coated particle will be chosen to be based on its hydrolysis rate in the body, as is well-known in the art, and not by mechanical shear or deformation as could occur in a particle coated with a lamellar coating. Since most production protocols used in industrial or pharmaceutical practice involve shear, release upon the application of such shear rates to a lamellar-coated particle system could be detrimental or disastrous in the context of such a process.

Detailed Description Text (117):
As is well-known in the art, in the case of polymers, polymers universally have amorphous domains: no polymer is ever 100% crystalline, and thus even high-crystallinity polymers are semi-crystalline and possess a finite fraction of amorphous domains. Often this is in the range of about 1-50%. The glass transition temperature of these amorphous domains can usually be detected by thermodynamic (e.g., DSC) techniques or rheometric measurements, though in certain very high-crystallinity polymers (greater than about 98%), this may be a difficult undertaking. Nevertheless, even in these high-crystallinity cases the amorphous domains can play important roles: they can mitigate structural problems associated with microcrystallite boundaries, thus conferring greater homogeneity and cohesiveness to microcrystalline polymers; this in turn can have strong effects on rheological properties and behavior as diffusional barriers; according to the fringed micelle model, an amorphous domain can provide a medium that allows for a single chain to extend through several microcrystallites, yielding a physical crosslinking (analogous to the physical crosslinking that occurs in thermoplastic elastomers); and their presence may in fact allow for crystallinity in high-MW polymers where the amorphous domains are the necessary result of chain folding. Being amorphous, these domains are non-lamellar regions in the polymer that are distinct from the crystalline regions but nonetheless actually play crucial roles in the crystallization of polymers and in determining their overall properties.

Detailed Description Text (129):
In general, small-molecule amorphous materials tend to exhibit lessor stability over time than their corresponding crystalline materials. In particular, a small-molecule

amorphous material will often show a tendency to revert to a crystalline form over a period of time that is comparable to, or shorter than, timescales that are relevant for the storage and use of a product. In the case of high-MW polymers, even though the true equilibrium condition may be a crystal, kinetics of rearrangement can be so slow that the timescale required for attainment of this equilibrium is for all intents and purposes infinite, so that the material can be locked into an amorphous or semi-crystalline state. For certain applications, this may be highly desirable. For example, many of the well-known elastomers and plastics, such as natural rubber (an example of an elastomer) or polymethylmethacrylate (PMMA, also known as Plexiglass, an example of a thermoplastic), are amorphous materials.

Detailed Description Text (130):
Semi-crystalline materials can in certain ways offer significant advantages, though their occurrence as long-lasting states is largely limited to high-MW polymers. A semi-crystalline polymer with high crystallinity can offer high modulus due to the preponderance of crystalline domains, but a certain amount of ductility due to the presence of amorphous domains, which can absorb stress without cracking. A number of the most important polymers, both commodity and engineering plastics, are semi-crystalline.

Detailed Description Text (145):
Other examples of uses of coated particles of the present invention include: 1. Paints and inks. Including Microencapsulation of pigments; Cationic charging of pigments (where pH-dependence can be important); Fillers and texturizing agents for non-aqueous paints; 2. Paper. Including Microcapsular opacifiers (also in paints); Pressure-sensitive ink microcapsules for carbonless copying paper; 3. Non-wovens. Including Additives that adhere to fibers throughout processing; 4. Agricultural. Including controlled release of pheromones (some of which are otherwise volatile or environmentally unstable if not encapsulated) for insect control; Controlled release of insect chemosterilants and growth regulators (many of which are otherwise environmentally unstable): Controlled release of other pesticides (with temperature independence being important); Controlled release of herbicides; Encapsulation of the plant growth regulators ethylene and acetylene (that are otherwise volatile); Taste modifiers to deter mammalian pests (e.g. capsaicin), Nutrient and fertilizer release; 5. Environment and forestry. Including Controlled release of aquatic herbicides for weed control; Controlled release of other herbicides; Controlled release of nutrients in agriculture; Soil treatment and nutrient release; Encapsulation and release of chelating agents (e.g., for heavy metal contaminants): Control of deposition and environmental fate of actives (viz., through targeted release of crystal coating and/or adhesive property of cubic phase): Encapsulation of hygroscopic or other (e.g., urea and sodium chloride) "seeding" agents for meteorological control; 6. Vaccines. Including HIV gag, gag-pol transfection of cells as an example; Adjuvants for the proper presentation of antigens or antibodies; 7. Nuclear medicine. Including Separation of two (otherwise mutually-destructive) radionuclides into separate particles for treatment of cancer; 8. Cosmetics. Including Antioxidant, Antiaging skin cream: Separation of two components of an antiacne medication; Suntan lotions with encapsulated prostaglandins and vitamins; Encapsulation of fat-soluble vitamins, oxidatively sensitive vitamins, vitamin mixes; Encapsulation of volatile perfumes and other odorants; Encapsulated volatile perfumes for scratch and sniff advertisements, Encapsulation of volatile make-up removers or other cosmetics for sheet formation; Encapsulated solvents for nail polish removers (or the polish itself ); Aerosol particles containing encapsulated hair dye; Sanitary napkins containing encapsulated deodorant; 9 Veterinary. Including Controlled release of volatile anti-flea compounds; Encapsulated feed additives for ruminants; Encapsulation of anti-microbial and insecticides in animal husbandry; 10. Dental. Including Controlled-release dentifrice components, particularly hydrolytically unstable anti-calculus compounds; Delivery of oral anti-cancer compounds (photophyrin); 11. Polymerization catalysts in one-pot (single-package) resin systems; 12. Household Products. Including controlled-release air fresheners, perfumes; Controlled-release insect repellants; Laundry detergents (e.g., encapsulated proteases); Other detergency applications; Softeners; Fluorescent brighteners; 13. Industrial. Including encapsulation of phosphine, ethylene dibromide, etc. volatiles for fumigating stored products; Catalytic particles; Activated charcoal microparticles for sorption and purification, 14. Polymer additives. Including polymer additives

for protection of wires,paper cartons etc, from rodents; Impact modifiers; Colorants and opacifiers; Flame retardant and smoke suppressants; Stabilizers; Optical brighteners; Limitations in current polymer-based encapsulation of additives include low melting point (during processing, polymer-polymer incompatibility, particle size limitations, optical clarity, etc. Some polymer additives used for lubrication of the polymer are based on waxes, which suffer from low melting point, except for certain synthetic waxes which are expensive; 15. Food and beverage processing. Including Encapsulation of (volatile) flavors, aromas, and oils (e.g., coconut, peppermint); Encapsulation of vegetable fats in cattle feeds; Encapsulated enzymes for fermentation and purification (e.g., diacetyl reductase in beer brewing); Encapsulation as an alternative to blanching, for improved lifetime of frozen foods; Microencapsulated tobacco additives (flavorings); pH-triggered buffering agents; Removal of impurities and decolorization using activated charcoal encapsulated in a porous material; 16. Photographics. Including Fine-grain film with dispersions of submicron photoreactive particles; Faster Film due to optical clarity (and thus higher transmission) and shorter diffusion times of submicron dispersion; Microencapsulation of photoprocessing agents; 17. Explosives and propellants. Including both liquid and solid propellants and explosives are used in encapsulated form; also, water is used in encapsulated form as a temperature moderator in solid propellants; 18. Research. Including Microcapsule-packed columns in extractions and separations; Biochemical assays, particularly, in pharmaceutical research and screening; 19. Diagnostics. Including encapsulated markers for angiography and radiography and clinical assays involving milieu-sensitive proteins and glycolipids; indeed, particles incorporating certain radiopaque or optically dense materials could themselves be used for imaging, and when coupled to targeting compounds as described herein could target specific sites in the body and allow their visualization.

Detailed Description Text (149):
Alternatively, the coated particle can be made by one of the following processes: providing a volume of the matrix that includes a material in solution in it that is capable of forming a nonlamellar material that is insoluble in the matrix and causing the aforesaid material to become insoluble in the matrix and subdividing the volume into particles by the application of energy to the volume; dispersing particles of said matrix into a fluid that includes at least one chemical species having a moiety capable of forming a nonlamellar material upon reaction or association with a second moiety and adding to said dispersion at least one chemical species having said second moiety to react said first moiety with said second moiety; dispersing particles of said matrix into a fluid that includes at least one chemical species having a moiety capable of forming a nonlamellar material upon reaction or association with a second moiety, adding to said dispersion at least one chemical species having said second moiety to react said first moiety with said second moiety, and subdividing the resulting material into particles by the application of energy to said material; dispersing a volume of said matrix in a form of said nonlamellar material selected from the group consisting of liquefied form, solution, or fluid precursor, and solidifying said nonlamellar material by a techniques selected from the group consisting of cooling, evaporating a volatile solvent, or implementing a chemical reaction; dispersing or dissolving a volume of said matrix in a liquid comprising said nonlamellar material in solution or dispersed form and comprising also a volatile solvent, and spray-drying said solution or dispersion; or applying spray-drying, electrospinning, or other comparable process to a solution or dispersion that contains the components of both the matrix and the coating. Or, a combination of these processes can be used.

Detailed Description Text (157):
In other embodiments of the present invention, advantages can be obtained by using a precursor to the coating material that localizes preferentially the surface of particles of the nanostructured liquid or liquid crystalline matrix, and dispersing the nanostructured liquid or liquid crystalline phase-often with the aid of this surface-localized precursor-prior to converting this precursor to the actual coating material. This is especially preferred in the case where a surface-active precursor can be found, or when the precursor can otherwise be substantially localized near the surface of the dispersed particles, by a favorable interaction with another component (ionic pairing, hydrogen bonding, etc.), or by a non-specific effect such as the hydrophobic effect, or by selecting a precursor or precursor-containing

solution with the proper surface energy. When this can be achieved, as it is in Example 41 below, then the localization of the precursor at the particle surface can be maintained throughout its conversion to the coating resulting in good intimacy between the particle and coating and efficient use of the coating material. In Example 41, the sodium salt of N-acetyltryptophan, which is a surface-active compound (due to the hydrophobicity of N-acetyltryptophan, augmented by the polarity of the ionized carboxylate group at one end), is used to disperse a cubic phase into microparticles with a particle surface that is rich in this precursor to the final coating material, which in this case is the zinc salt of N-acetyltryptophan. This is a very general approach, for example since the most useful coating materials are of course of low solubility in water, and thus each possesses at least one dominant hydrophobic group, but also has at least one polar group that allows it to have sufficient solubility or interaction with water in some precursor state; this is in fact tantamount to saying that it is an amphiphile, or even a surface-active compound, in this precursor state (or that such a state can be found). Other approaches for localizing the precursor at the particle surface include: ion-pairing the precursor to an oppositely-charged molecule that partitions strongly into the cubic phase; using a melted or solubilized form of the precursor such that the surface energy of the melted precursor or precursor solution favors its localization in between the nanostructured phase and the exterior phase in which the nanostructured phase is dispersed; choosing a precursor that has favorable interactions such as extensive hydrogen bonding with the nanostructured phase surface, particularly in the case where the precursor (and coating) is a polymer, so that it is by virtue of its high MW excluded from the interior of the nanostructured phase particle; invoking specific interactions such as antibody-antigen or receptor-ligand interactions; and using a precursor, preferably a polymer or biomacromolecule (protein, nucleic acid, polysaccharide, etc.) that is substantially insoluble in the nanostructured phase but contains hydrophobic anchor groups that partition into the nanostructured phase, where such hydrophobic anchors are known in the art and typically are alkanes or cholesterol-derivatives that are grafted onto the polymer or biomacromolecule.

Detailed Description Text (160):
As discussed above, in certain embodiments of this invention the interior matrix will be a dehydrated variant of the desired phase, that will form the desired nanostructured liquid or liquid crystalline phase upon contact with a water-containing fluid. There are three general ways in which such a particle can be produced. One is to use a process similar to that used in Example 42, where a matrix or, in this case dehydrated matrix, is dispersed in a non-aqueous solution or melt that is, or contains, a precursor of the coating material; upon cooling or otherwise converting this precursor to the coating, the dehydrated matrix would then be the encapsulated entity. A second general method is to apply a drying process, such as freeze-drying, electrospinning, or preferably spray-drying, to a water-containing dispersion of the particles in which the coating material (or a precursor thereof) has been dissolved or very finely dispersed. And a third general method is to dissolve or disperse all the components of the coating and of the matrix, either including or excluding the water, in a volatile solvent and applying a drying process, again preferably spray-drying. Several of these methods can avoid the use of water completely, which would be important in the case of actives (or special excipients) that should not contact water even during production.

Detailed Description Text (162):
The utilization of amorphous and semi-crystalline materials as exterior coatings in the instant invention makes it all the more practical to incorporate, in a number of different ways, chemicals or chemical groups that can be invoked to target particles temporally and spatially, for example, to target particles to specific sites in the body. Similarly, other bioactive compounds incorporated on or in the coating could serve important functions, such as: absorption enhancers such as menthol could be present so as to increase permeability of absorption barriers (lipid bilayers, gap junctions) prior to or concomitant with the release of drug; proteins or other adsorption-modulating materials could be incorporated that would inhibit unfavorable binding of endogenous proteins such as albumin; adjuvants could be incorporated that would enhance the effect of vaccine components or other immune modulating materials. In general, an amorphous or semi-crystalline material can, for example, incorporate molecules or even submicron solids as embedded materials, more readily and

efficiently than with crystalline materials which tend to exclude other materials during their crystallization--particularly when the crystallization is performed in accordance with the tight regulations that govern the pharmaceutical industry. Furthermore, covalent or ionic attachment of organic groups to polymers at their surfaces is a well-developed art. U.S. Pat. Nos. 6,344,050 and 5,484,584 (incorporated herein by reference in their entirety) are examples of methods known in the art for attaching molecular targets to polymers and microparticle coatings in particular. Antibodies, steroids, hormones, oligo- or polysaccharides, nucleic acids, vitamins, immunogens, and even nanoprobes are all examples of a wide range of materials that could be attached to particles of the instant invention with an exterior phase of amorphous, semi-crystalline, or less likely crystalline, material.

Detailed Description Text (164):
While it is not always crucial for a given application to know the exact localization (or more precisely, the spatial probability distribution) of a targeting moiety within or in association with a particle, this may be an important consideration in the design of a particle-targeting moiety combination, and the instant invention lends itself to a good deal of flexibility and power in this respect. Typically, targeting moieties could be substantially localized at one or more of the following sites in reference to the coated microparticle: 1) in the interior of the particle, i.e., dissolved or dispersed in the nanostructured liquid or liquid crystalline phase interior; this locality can offer the distinct advantage of providing a "biomimetic" milieu for the targeting moiety, a milieu which can comprise a lipid bilayer as well as hydrophilic domains each of which can be tuned to optimize the environment; 2) at the outer surface of the interior--particularly if there is a distinct phase in between the interior phase and exterior coating, such as an aqueous layer; such a location could be particularly advantageous for a particle that would present its targeting moiety at the new outer surface after release of the exterior coating; 3) adsorbed to the inner surface of the exterior coating; in this location, as well as in the other locations listed here, there may be a synergy between the solid shell and the targeting moiety, in that certain solid materials (such as aluminum-based compounds, for example) can sometimes act as adjuvants, to increase the effectiveness of molecules in the body particularly if they are meant to interact with the body's immune system; 4) embedded in the exterior coating, which as discussed above is most likely to be achievable if the coating is amorphous or at least semi-crystalline; 5) at the surface of the exterior coating, either adsorbed or bound via, e.g., covalent, ionic, hydrogen bonding, and/or hydrophobic interactions; 6) attached to, but at a distance from, the surface of the exterior coating, through attachment via a flexible spacer, e.g., a polymer that is attached (e.g. by covalently bonding) at one end to a component of the particle (interior or exterior) and at the other end to the targeting moiety. Experience with other types of microparticles in the art has shown that this is generally an excellent approach for achieving good targeting because it preserves important conformational and diffusional degrees of freedom that are sometimes required for good docking of a targeting moiety with a receptor or target.

Detailed Description Text (183):
Example 5 demonstrates that compounds such as sulfides and oxides can be used as coatings in the coated particles of the present invention, even when they require gaseous reactants for formation. Such compounds are well-known for being not only high-stiffness materials, but also chemically extremely resistant, which could make such coated particles of interest in applications where the particles encounter harsh chemical and physical conditions, such as would be expected in use of the particles as polymer additives, or in processing involving high shear, such as impregnation of dye-containing particles in nonwoven materials, etc.

Detailed Description Text (185):
Examples 39 and 40 demonstrate the use of amorphous materials as exterior coatings for the particles of the present invention. Example 39 utilizes the amorphous polymer (PLGA), and Example 40 utilizes a small molecule (the sugar trehalose).

Detailed Description Text (258):
Particles with coatings resistant to shear could be important in applications requiring pumping of the particles, where traditional polymer-coated particles are

known to suffer lifetime limitations due to degradation of the coating with shear.

Detailed Description Text (286):
The coating in this example may find use in the removal of heavy metals from industrial streams. In this case the coating can be a porous crystal--known as a clathrate--which permits atomic ions to pass across the coating and into the cubic phase interior, which is an extremely high-capacity absorbent for ions due to the high surface charge density (using an anionic surfactant, or more selective chelating groups such as bipyridinium groups, etc.). Most likely permanent pores would be the best. The selectivity afforded by the clathrate coating circumvents the reduction in sorbent power that is inevitable with traditional sorbents (such as activated carbon and macroreticular polymers), due to larger compounds that compete with the target heavy metal ions for the available adsorption sites. Regeneration of the sorbent could be by ion-exchange, while keeping the particles and coatings intact (this latter step would, incidently, be an example of release).

Detailed Description Text (305):
The microparticles were then immobilized in a polyacrylamide hydrogel. Acrylamide (0.296 grams), methylene-bis-acrylamide (0.024 grams, as crosslinker), ammonium persulfate (0.005 grams, as initiator), and tetramethylethylene diamine (TMED, 0.019 grams, as co-initiator) were added to the dispersion, resulting in polymerization of the acrylamide into a crosslinked hydrogel in less than 30 minutes. A thin slice of the hydrogel was examined under a microscope, and a high concentration of microparticles was seen, just as with the original dispersion.

Detailed Description Text (310):
The microparticles were then immobilized in a polyacrylamide hydrogel. Acrylamide (0.365 grams), methylene-bis-acrylamide (0.049 grams, as crosslinker), ammonium persulfate (0.072 grams of a 2% solution, as initiator), and tetramethylethylene diamine (TMED, 0.011 grams, as co-initiator) were added to the dispersion, resulting in polymerization of the acrylamide into a crosslinked hydrogel in a matter of hours. A thin slice of the hydrogel was examined under a microscope, and a high concentration of microparticles was seen (except near the very bottom of the hydrogel), just as with the original dispersion.

Detailed Description Text (329):
The particles in this Example bear a structural relationship with polymer-encapsulated liposomes, but do not suffer from the harsh chemical conditions used to produce polymer-encapsulated liposomes; the ability to produce, in a single step, lamellar phase-interior particles coated with a wide range of crystalline coatings, and under mild conditions, could make the present invention of importance in controlled release drug delivery.

Detailed Description Text (376):
A poly(lactic-glycolic acid) polymer (PLGA), with a 59:41 lactide:glycolide ratio and an inherent viscosity of 0.51 dl/gm, was obtained from Purac Biochem (The Netherlands). This copolymer is known to be amorphous, and this was evidenced by lack of birefringence. An amount 0.307 grams of this polymer was dissolved in 3.002 gm of ethyl acetate. A cubic phase was prepared by mixing 0.042 grams of the prothrombogenic compound menadione, 0.272 grams of oil of ginger, 0.224 grams of water, and 0.540 grams of the ethoxylated hydrogenated castor oil surfactant Arlatone G (obtained from Uniquema). This was heated to 50.degree. C. in order to dissolve the menadione. An amount 0.302 grams of this cubic phase was added to a second 16 ml glass tube, overlaid with 9.707 ml of water, and dispersed into the water by shaking. The PLGA solution was added to the cubic phase dispersion, the mixture shaken immediately, and sonicated for 10 minutes. Following this, the contents were transferred into a round bottom flask, placed on a rotovap apparatus, and evaporated to a final volume of approximately 9.7 ml.

CLAIMS:

37. The coated particle of claim 1 wherein said nonlamellar domain is a polymer.

38. The coated particle of claim 37 wherein said polymer is PLGA.